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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/120,030	07/21/1998	BETH P GOLDSTEIN	7732-022-27	1743

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EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/120,030	Applicant(s) Goldstein et al.
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 4, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 5, 28, 32-39, and 41-55* is/are pending in the application.

4a) Of the above, claim(s) *28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 5, 32-39, and 41-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *4, 5, 28, 32-39, and 41-55* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/4/01 has been entered.

Status of Claims

2. Claims 29,40 are canceled. Claims 4,5,28,35 are amended. Claims 4,5, 28,32-39, 41-55 are pending.

Further restriction

Upon further consideration of the amended claims the following additional restriction of was deemed necessary.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 4,5,32-39, 41-55, drawn to method of treating staphylococcal infection by systemic administration of lysostaphin.

II. Claim 32, drawn to pharmaceutical composition of lysostaphin.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the composition of Group II can be used in a materially different processes such as treating staphylococcal infection with lysostaphin administered via non-systemic routes (e.g., topical). The intended use recited now in the claim does not distinguish it from any other composition comprising recombinant lysostaphin.

Further, a reference teaching a composition comprising recombinant lysostaphin would not necessarily teach or suggest its systemic use.

As the applicant's intention to examine claims drawn to systemic administration clearly follows from amendments to the claims reciting such administration, Group I is considered as constructively elected. Claim 28 is withdrawn from consideration as drawn to non-elected Group.

Claims 4,5,32-39, 41-55 are addressed in this Office action.

Claim Rejections - 35 USC § 103

3. Claims 4, 5 are rejected are rejected under 35 U.S.C. 103(a) as obvious over Stark and Zygmunt in view of Oldham. The rejection is maintained for the reasons of record:

The instant claims are drawn to method of treating staphylococcal infection comprising administering effective amount of at least one recombinantly produced lysostaphin analog and to the pharmaceutical composition comprising the recombinantly produced lysostaphin analog. A lysostaphin analog is defined as recombinantly produced lysostaphin, its mutant variants or any related enzyme that retains proteolytic activity.

Stark (N.Engl. J. Med, 291, 239-240, 1974; see specification, p. 3, lines 21-25).

Stark et al describes systemic administration of lysostaphin to a man suffering from staphylococcal pneumonia resulting from terminal unresponsive leukemia. The reference demonstrates that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with 500 mg of lysostaphin rapidly

cleared microorganisms from pustule sites. The treatment removed staphylococci from blood, lungs, or abscess site.

Zygmunt

Zygmunt et al is a more general reference reviewing properties of lysostaphin and its *in vitro* and *in vivo* applications. The reference teaches that lysostaphin is effective against a wide variety of staphylococcal infection, and is more potent than penicillins. Lysostaphin is effective against strains of S. Aureus which are insensitive to other antimicrobial agents, such as cloxacillin, oxacillin, cephalothin (p. 314), and in particular, strains insensitive to methicillin (p. 314,316,317). Similar to its *in vitro* effect, lysostaphin is effective *in vivo* against a wide variety of staphylococcal infections. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-325). The dosage of lysostaphin varies in the range of 0.5 to 50 mg/kg (p. 320, Table 4). The ways of administration are intravenous, intraperitoneal, topical, intranasal (pages 319-324). Combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322). The reference also teaches pharmaceutical compositions comprising lysostaphin.

The primary references do not teach recombinant lysostaphin or use thereof. It is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Oldham

Oldham et al teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin, at low concentration of 5 μg/ml, is effective against *S. Aureus* in mammary tissue. See abstract.

It would have been obvious to one skilled in the art at the time the invention was made to be motivated to use recombinant lysostaphin instead of the natural lysostaphin used in the primary references (e.g., in the systemic treatment described by Stark et al.), because it is easier to produce a recombinant analog of a natural product and because Oldham demonstrated that recombinant lysostaphin has high antimicrobial activity, similar to the natural product.

Further, in regard to lysostaphin analogs and use thereof, it is well known in the pharmaceutical art to develop and use new, improved analogs of known pharmaceuticals. As mechanism of action of lysostaphin is the lysis of the membrane

wall of staphylococci, it would be obvious to develop and use new, more potent analogs of this well known antibiotic. Specification, p. 1, lines 26-34, is cited to exemplify lysostaphin analogs known in the prior art.

In regard to various locations of treatment, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

Response to arguments[1]

Applicant argues that in the case described in Stark the treatment is more speculative than conclusive. The reference, however, teaches that a single systemic treatment with 500 mg of lysostaphin rapidly cleared microorganisms from pustule sites. Further, applicant argues that because the patient died, the reference does not demonstrate long-term results. The instant claims, however, are not drawn to a treatment of any certain duration.

[1]Both the applicant's response and Declaration of Climo are addressed.

In regard to Zygmunt reference, the reference is used as providing general teaching on lysostaphin and demonstrating benefits of its use with other antimicrobials.

In regard to Oldham reference, applicant argues that the recombinant lysostaphin is demonstrated as highly immunogenic. It is not clear, however, how recombinant lysostaphin is different from natural in anything but its origin. As for the discussed immunogenecity, it has been already well documented for natural lysostaphin. However, first, the prior art does not assert that immunogenecity demonstrated on animals precludes from systemic administration to humans. Contrary, Stark demonstrates systemic administration to human. Further, even for animals, the prior art demonstrates that even though lysostaphin immunogenecity is a known factor, infection in animals can be successfully treated with lysostaphin. Thus, Zigmunt describes that, although systemic administration of lysostaphin triggered generation of antibodies to lysostaphin, subsequent administration of lysostaphin did not cause adverse reactions (p. 326, last full paragraph). Same section of the reference describes that in the absence of adjuvant, lysostaphin does not cause formation of antibodies or death of animals. In regard to observation of Oldham on immunogenicity of recombinant lysostaphin, the same research group, in their next year's publication (Daley & Oldham, Veterinary Immunology and Immunopathology, (1992 Mar) 31 (3-4) 301-12) reported that "infusion of

recombinant lysostaphin does not elicit any observable effects on the host animal or on the potential efficacy of the recombinant molecule. As for the argument that described treatment in Oldham can not be extrapolated to humans, the rejection does not attempt to make such extrapolation. Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Applicant argues that it would not have been obvious to use recombinant lysostaphin (or its analogs) instead of lysostaphin (or its analogs) produced by non-recombinant methods. Broad spectrum antimicrobial effect of lysostaphin is well established in the art. Further, it is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification).

The argument that Oldham demonstrates activity of recombinant lysostaphin only in mammary tissue is not convincing. While it may not be absolutely certain that recombinant lysostaphin will be as effective in treatment of infections in other locations as in mammary tissue, a *prima facie* case of obviousness does not require absolute predictability of success. See In re O'Farell, 7 USPQ2d 1673 (CAFC 1988). In view of the similarity of effects of recombinant and non-recombinant lysostaphins in mammary tissue, and in view of the known broad range of antimicrobial activity of

lysostaphin, effectiveness of recombinant lysostaphin (or its analogs) would have been expected to be similar in other sites of microbial infection as well.

4. Claims 32,35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt or Stark or Goldberg in view of Oldham as applied to claims 4,5, above, and further in view of Dixon.

The instant claims are drawn to combination therapy of lysostaphin and another antimicrobial, in particular rifamycin or a glycopeptide. The primary references do not teach combined use of lysostaphin and rifamycin or a glycopeptide. However, Zygmunt teaches that a single dose of lysostaphin is effective against staphylococcal infection only for limited time, and it is preferable to follow lysostaphin with another antibiotic. Dixon et al. teach that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction. See p. 63, first paragraph. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the lysostaphin not only as a sole active pharmaceutical agent, but also in

combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

Response to arguments

Applicant argues that the prior art describes sequential administration of components of combined therapy, whereas the instant invention is drawn to simultaneous administration. First, the instant claims are not drawn to simultaneous administration. Administering "together" (as in claim 32) does not mean administering simultaneously. Further, specification teaches that administration can be either alternating or simultaneous (p. 4, line 20). Furthermore, the examples in specification illustrate sequential, rather than simultaneous administration (see, e.g., p. 21, Table 6, last row). In addition, there is no demonstration of combined simultaneous systemic administration of two antibiotics to humans.

5. Claims 33,34, 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt and Stark and Goldberg and Oldham.

The instant claims are drawn to particular dosage ranges. The primary references teach use of different dosages and different ways of administration of lysostaphin. If there are any differences between dosage ranges as claimed and that of the prior art, the differences would be appear minor in nature. Absent some

teaching to the contrary, determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization.

Response to arguments

Applicant argues that dosage range for lysostaphin is demonstrated for natural, not recombinant, lysostaphin. No evidence, however, is presented that lysostaphin produced recombinantly (i.e., natural lysostaphin recreated recombinantly) is any different from natural lysostaphin.

Conclusion.

6. No claims are allowed

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER